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PATENT- OG VAREMÆRKESTYRELSEN

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NOVEL QUINUCLIDINE DERIVATIVES AND THEIR USE

TECHNICAL FIELD

This invention relates to novel quinuclidine derivatives and their use as pharmaceuticals.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

BACKGROUND ART

The endogenous cholinergic neurotransmitter, acetylcholine, exerts its biological effect via two types of cholinergic receptors, the muscarinic Acetyl Choline Receptors (mAChR) and the nicotinic Acetyl Choline Receptors (nAChR).

It is well established that muscarinic acetylcholine receptors are of importance in relation to memory and cognition, and much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic acetylcholine receptor modulators.

Recently, however, an interest in the development of nicotinic acetylcholine receptor modulators has emerged. Several diseases are associated with degeneration of the cholinergic system, i.e. senile dementia of the Alzheimer type, vascular dementia and cognitive impairment due to the organic brain damage disease related directly to alcoholism.

Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency.

SUMMARY OF THE INVENTION

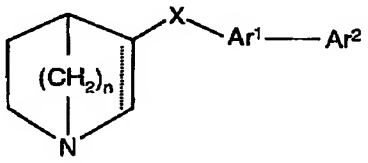
The present invention is devoted to the provision of new quinuclidine derivatives that are modulators of the nicotinic and/or of the monoamine receptors, and which modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors, and in particular the nicotinic acetylcholine receptor, the monoamine receptors, in particular the serotonin receptor (5-HTR), the dopamine

receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE).

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

The compounds of the invention may also be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging), and they may be used in labelled or unlabelled form.

Accordingly, in its first aspect the invention provides quinuclidine derivatives represented by Formula I



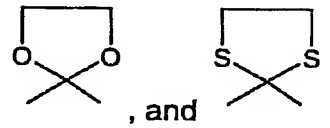
(I)

enantiomers thereof, or mixtures of its enantiomers, or a pharmaceutically-acceptable addition salts thereof, or onium salts thereof, wherein,

------ represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -S-, $-CH_2-$, $-C(=CH_2)-$,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and ;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl; and

Ar^2 represents an optional aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl.

In another aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the quinuclidine derivative of the invention.

In a third aspect the invention relates to the use of the quinuclidine derivative of the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the action of a nicotinic acetylcholine receptor modulator.

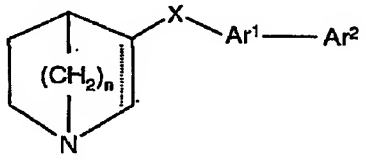
In a further aspect the invention provides a method of the treatment or alleviation of a disease or disorder of a living animal body, including a human, which disease or disorder is responsive to the action of a nicotinic acetylcholine receptor modulator, which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of the quinuclidine derivative of the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Quinuclidine Derivatives

In its first aspect, the present invention provides novel quinuclidine derivatives represented by Formula I



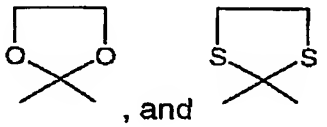
(I)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

------ represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -S-, $-CH_2-$, $-C(=CH_2)-$,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and ;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl; and

Ar^2 represents an optional aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl.

In a preferred embodiment the aromatic monocyclic or polycyclic, carbocyclic group (i.e. Ar^2 and/or Ar^1) is phenyl, indenyl, naphthyl, azulenyl, fluorenyl, or anthracenyl.

In another preferred embodiment the aromatic monocyclic heterocyclic group (i.e. Ar^2 and/or Ar^1) is an aromatic 5- or 6-membered heterocyclic group holding nitrogen (N), oxygen (O), sulphur (S) and/or seleno (Se) as heteroatom(s).

In a third preferred embodiment the aromatic monocyclic heterocyclic group (i.e. Ar^2 and/or Ar^1) is furanyl, in particular 2- or 3-furanyl; thienyl, in particular 2- or 3-thienyl; selenophenyl, in particular 2- or 3-selenophenyl; pyrrolyl (azolyl), in particular 2 or 3-pyrrolyl; oxazolyl, in particular oxazol-2,4 or 5-yl; thiazolyl, in particular thiazol-2,4 or 5-yl; imidazolyl, in particular 2 or 4-imidazolyl; pyrazolyl, in particular 3 or 4-pyrazolyl; isoxazolyl, in particular isoxazol-3,4 or 5-yl; isothiazolyl, in particular isothiazol-3,4 or 5-yl; oxadiazolyl, in particular 1,2,3-oxadiazol-4 or 5-yl, or 1,3,4-oxadiazol-2-yl; triazolyl, in particular 1,2,3-triazol-4-yl or 1,2,4-triazol-3-yl; thiadiazolyl, in particular 1,2,3-thiadiazol-4 or 5-yl, or 1,3,4-thiadiazol-2-yl; pyridinyl, in particular 2,3 or 4-pyridinyl; pyridazinyl, in particular 3 or 4-pyridazinyl; pyrimidinyl, in particular 2,4 or 5-pyrimidinyl; pyrazinyl, in particular 2 or 3-pyrazinyl; and triazinyl, in particular 1,2,4- or 1,3,5-triazinyl.

In a fourth preferred embodiment the aromatic polycyclic heterocyclic group (i.e. Ar^2 and/or Ar^1) is a bi- or poly-heterocyclic heterocyclic group, which groups include benzo-fused 5- and 6-membered heterocyclic rings containing one or more heteroatoms, selected from nitrogen (N), oxygen (O) and/or sulphur (S).

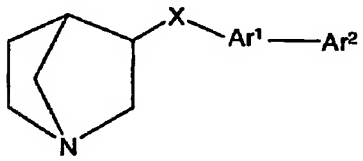
In a fifth preferred embodiment the bicyclic aromatic heterocyclic group (i.e. Ar^2 and/or Ar^1) is indolyl, in particular 2 or 3-indolyl; isoindolyl, in particular 1 or 3-isoindolyl; benzo[b]furanyl, in particular 2 or 3-benzo[b]furanyl; benzo[b]thienyl, in particular 2 or 3-benzo[b]thienyl; benzoimidazolyl, in particular 2-benzoimidazolyl; benzothiazolyl, in particular 2-benzothiazolyl; quinolinyl, in particular 2,3 or 4-quinolinyl; isoquinolinyl, in particular 1,3 or 4-isoquinolinyl; cinnolinyl, in particular 3 or 4-

cinnolinyl; phthalazinyl, in particular 1 or 4-phthalazinyl; quinazolinyl, in particular 2 or 4-quinazolinyl; quinoxalinyl, in particular 2 or 3-quinoxalinyl.

In a sixth preferred embodiment the aromatic group (i.e. Ar^2 and/or Ar^1) is a polycyclic aromatic heterocyclic group selected from fluorenone, dibenzothiophene and dibenzothiophene-5,5-dioxide.

In a seventh preferred embodiment the aromatic group (i.e. Ar^2 and/or Ar^1) is substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen.

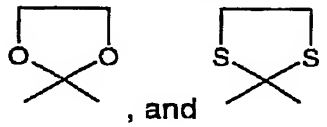
In another preferred embodiment the quinuclidine derivative of the invention is represented by Formula II



(II)

wherein

X represents a linker selected from -O-, -S-, $-CH_2-$, $-C(=CH_2)-$,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and ;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl; and

Ar^2 represents an optional aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl.

In a preferred embodiment the quinuclidine derivative of the invention is a compound of Formula II, wherein

X represents O, S or CH_2; and

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic group selected from phenyl and naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic 5- or 6-membered monocyclic heterocyclic group selected from 1,3,4-thiadiazol-2-yl, pyridazinyl, in particular 2-pyridazinyl, which aromatic monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic bicyclic heterocyclic group selected from quinolinyl, in particular 2-quinolinyl; benzothiazolyl, in particular 2-benzothiazolyl; quinoxalinyl, in particular 2-quinoxalinyl; benzoimidazolyl, in particular 2-benzoimidazolyl; and benzoxazolyl, in particular 2-benzoxazolyl, which aromatic bicyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; and

Ar^2 represents phenyl or naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen.

In another preferred embodiment the quinuclidine derivative of the invention is a compound of Formula II, wherein

X represents O, S or CH_2; and

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic group selected from phenyl and naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

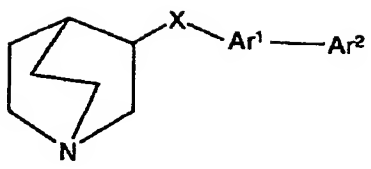
Ar^1 represents an aromatic 5- or 6-membered monocyclic heterocyclic group selected from 1,3,4-thiadiazol-2-yl, pyridazinyl, in particular 2-pyridazinyl, which aromatic monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic bicyclic heterocyclic group selected from quinolinyl, in particular 2-quinolinyl; benzothiazolyl, in particular 2-benzothiazolyl; quinoxalinyl, in particular 2-quinoxalinyl; benzoimidazolyl, in particular 2-benzoimidazolyl; and benzoxazolyl, in particular 2-benzoxazolyl, which aromatic bicyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents a polycyclic aromatic heterocyclic group selected from fluorenone, dibenzothiophene or dibenzothiophene-5,5-dioxide; and

Ar^2 is absent.

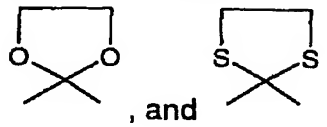
In another preferred embodiment the quinuclidine derivative of the invention is a compound of Formula III,



(III)

wherein,

X represents a linker selected from -O-, -S-, $-CH_2-$, $-C(=CH_2)-$,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and ;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl; and

Ar^2 represents an optional aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl.

In a preferred embodiment the quinuclidine derivative of the invention is a compound of Formula III, wherein

X represents O, S or CH_2;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic group selected from phenyl and naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic 5- or 6-membered monocyclic heterocyclic group selected from 1,3,4-thiadiazol-2-yl, pyridazinyl, in particular 2-pyridazinyl, which aromatic monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic bicyclic heterocyclic group selected from quinolinyl, in particular 2-quinolinyl; benzothiazolyl, in particular 2-benzothiazolyl; quinoxalinyl, in particular 2-quinoxalinyl; benzoimidazolyl, in particular 2-benzoimidazolyl; and benzoxazolyl, in particular 2-benzoxazolyl, which aromatic bicyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; and

Ar^2 represents phenyl or naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen.

In a most preferred embodiment the quinuclidine derivative of Formula III is

3-(Biphenyl-4-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(Biphenyl-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(Biphenyl-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(5-Phenyl-[1,3,4]oxadiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(5-Phenyl-[1,3,4]thiadiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(2-Phenyl-pyrimidin-5-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(5-Phenyl-pyrimidin-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(6-Phenyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(6-Benzyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(6-Phenoxy-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane; or

3-(6-Phenylsulfanyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

or an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

In another preferred embodiment the quinuclidine derivative of the invention is a compound of Formula III, wherein

X represents O, S or CH_2; and

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic group selected from phenyl and naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic 5- or 6-membered monocyclic heterocyclic group selected from 1,3,4-thiadiazol-2-yl, pyridazinyl, in particular 2-pyridazinyl, which aromatic monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic bicyclic heterocyclic group selected from quinolinyl, in particular 2-quinolinyl; benzothiazolyl, in particular 2-benzothiazolyl; quinoxalinyl, in particular 2-quinoxalinyl; benzoimidazolyl, in particular 2-benzoimidazolyl; and benzoxazolyl, in particular 2-benzoxazolyl, which aromatic bicyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents a polycyclic aromatic heterocyclic group selected from fluorenone, dibenzothiophene or dibenzothiophene-5,5-dioxide; and

Ar^2 is absent.

In a most preferred embodiment the quinuclidine derivative of Formula III is

(±)-3-(Naphthalen-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(Benzoxazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Chloro-benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1*H*-Benzoimidazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1-Methyl-1*H*-benzoimidazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Isoquinolin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoline;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinazoline;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoxaline;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-3-methoxy-quinoxaline;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-3-chloro-quinoxaline;
(±)-3-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-cinnoline; or
(±)-3-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-benzo[1,2,4]triazine;

or an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

Definition of Substituents

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18}-alkyl), more preferred of from one to six carbon atoms (C_{1-6}-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the invention include methoxy and ethoxy.

In the context of this invention a cycloalkoxy group designates a "cycloalkyl-O-" group, wherein cycloalkyl is as defined above.

In the context of this invention an alkoxy-alkyl group designates an "alkyl-O-alkyl-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkyl

groups of the invention include methoxy-methyl, methoxy-ethyl, ethoxy-methyl, and ethoxy-ethyl.

In the context of this invention an alkoxy-alkoxy group designates an "alkyl-O-alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkoxy groups of the invention include methoxy-methoxy, methoxy-ethoxy, ethoxy-methoxy, and ethoxy-ethoxy.

In the context of this invention a cycloalkoxy-alkyl group designates a "cycloalkyl-O-alkyl" group, wherein cycloalkyl and alkyl are as defined above.

In the context of this invention a cycloalkoxy-alkoxy group designates a "cycloalkyl-O-alkyl-O-" group, wherein cycloalkyl and alkyl are as defined above.

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms (±). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by

treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Methods of Preparation

The quinuclidine derivatives of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

The 2,5-diazabicyclo[2.2.1]heptane derivatives of the present are found to be potent modulators of the monoamine receptors and transporters.

In the context of this invention the term "a monoamine receptor modulator" covers compounds binding to a monoamine receptor, in particular the serotonin receptor, the dopamine receptor and/or the norepinephrine receptor, as well as compounds binding to the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and/or norepinephrine (NE).

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases,

PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

In a preferred embodiment the compounds of the invention are used for the treatment of diseases, disorders, or conditions relating to the central nervous system. Such diseases or disorders includes anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

In another preferred embodiment the compounds of the invention may be useful for the treatment of diseases, disorders, or conditions associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

In yet another preferred embodiment the compounds of the invention may be useful for the treatment of endocrine disorders, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

In still another preferred embodiment the compounds of the invention may be useful for the treatment of neurodegenerative disorders, including transient anoxia and induced neurodegeneration.

In even another preferred embodiment the compounds of the invention may be useful for the treatment of inflammatory diseases, disorders, or conditions, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

In still another preferred embodiment the compounds of the invention may be useful for the treatment of mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain.

In this context "treatment" covers treatment, prevention, prophylactics and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a voluntary diminished intake of the addictive substance.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the 2,5-diazabicyclo[2.2.1]heptane derivatives of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the 2,5-diazabicyclo[2.2.1]heptane derivative together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by a person skilled in the art by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered

to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

In another aspect the invention provides methods of the treatment, prevention or alleviation of diseases or disorders or conditions of a living animal body, including a human, which disease or disorder is responsive to the action of a monoamine receptor modulator, and which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of the 2,5-diazabicyclo[2.2.1]heptane derivative of the invention.

In the context of this invention the term "treating" covers treatment, prevention, prophylaxis or alleviation, and the term "disease" covers illnesses, diseases, disorders and conditions related to the disease in question.

It is at present contemplated that a suitable dosage lies within the range of from about 0.1 to about 500 milligram of active substance daily, more preferred of from about 10 to about 70 milligram of active substance daily, administered once or twice a day, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

General remarks: All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

Method A

(±)-3-(Naphthalen-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound A1)

To a mixture of 2-naphthol (5.0 g, 34.5 mmol), (±)-3-quinuclidinol (2.94 g, 23.1 mmol), triphenylphosphine (9.0 g, 34.5 mmol) and tetrahydrofuran (100 ml) was added: diethylazodicarboxylate (5.4 ml, 34.5 mmol) at room temperature during 30 minutes. The reaction mixture was allowed to stir for 20 hours at 50°C. Aqueous sodium hydroxide (100 ml, 1 M) was added. The mixture was extracted with dichloromethane (3 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 3.7 g (43%). Mp 140.9-141.6°C.

Method B

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoline fumaric acid salt (Compound B1)

A mixture of (±)-3-quinuclidinol (2.0 g, 15.7 mmol), (±)-2-chloroquinoline (2.6 g, 15.7 mmol) and DMF (30 ml) was stirred at room temperature. Sodium hydride (0.94 g, 23.6 mmol, 60% in oil) was added in small portions. The reaction mixture was stirred for 1.5 hours at 50°C. Aqueous sodium hydroxide (50 ml, 1 M) was added followed by extraction with diethyl ether (3 x 50 ml). The combined ethereal phases were washed with aqueous sodium hydroxide (2 x 50 ml, 1 M). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 4.62 g (79%). Mp 160.0-160.5°C.

(±)-3-(6-Chloro-benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B2)

Was prepared according to procedure B from 2,6-dichlorobenzothiazole. Mp 203-205°C.

(±)-3-(Benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B3)

Was prepared according to procedure B from 2-chlorobenzothiazole. Mp 173.7-174.2°C.

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-3-chloro-quinoxaline fumaric acid salt (Compound B4)

Was prepared according to procedure B from 2.3-dichloroquinoxaline. Mp 120.8-122.1°C.

(±)-3-(1-Methyl-1*H*-benzoimidazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt

(Compound B5)

Was prepared according to procedure B from 2-chloro-1-methylbenzoimidazole. Mp 184.9-185.9°C.

(±)-3-(Benzoxazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B6)

Was prepared according to procedure B from 2-chlorobenzoxazole. Mp 187.2-188.8°C.

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoxaline fumaric acid salt (Compound B7)

Was prepared according to procedure B from 2-chloroquinoxaline. Mp 127.7-128.5°C.

(±)-3-(6-Phenylpyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B8)

Was prepared according to procedure B from 3-chloro-6-phenylpyridazine. Mp 168.5-172.0°C.

(±)-2-(1-aza-bicyclo[2.2.2]oct-3-yloxy)-3-methoxy-quinoxaline fumaric acid salt (Compound B9)

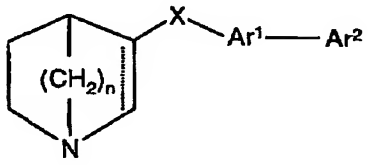
A mixture of (±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-3-chloro-quinoxaline (Compound B4; 1.38 g, 4.76 mmol), cecium carbonate (1.55 g, 4.76 mmol) and methanol (15 ml) was stirred for 3 hours at 45°C. Aqueous sodium hydroxide (50 ml, 1 M) was added followed by extraction with diethyl ether (3 x 50 ml). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.51 g, 27%. Mp 168.5-170.0°C.

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoxaline methylium iodide salt (Compound B10)

A mixture of (±)-3-(quinoxalin-2-yloxy)-1-aza-bicyclo[2.2.2]octane (1.27 g, 5.0 mmol) dichloromethane (10 ml) was added at -70°C: methyliodide (0.31 g, 5.0 mmol) solved in dichloromethane (1.5 ml) was added over 10 minutes. The reaction was stirred at -70°C for 40 minutes. The reaction mixture was allowed to stir at room temperature for 3 hours. The precipitate was isolated by filtration. Mp 229-230°C.

CLAIMS

1. A quinuclidine derivative represented by Formula I



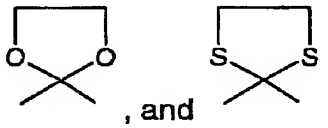
(I)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

------ represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -S-, $-CH_2-$, $-C(=CH_2)-$,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and ;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl; and

Ar^2 represents an optional aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl.

2. The quinuclidine derivative of claim 1, wherein the aromatic monocyclic or polycyclic, carbocyclic group is phenyl, indenyl, naphthyl, azulenyl, fluorenyl, or anthracenyl.

3. The quinuclidine derivative of claim 1, wherein the aromatic monocyclic heterocyclic group is an aromatic 5- or 6-membered heterocyclic group holding nitrogen (N), oxygen (O), sulphur (S) and/or seleno (Se) as heteroatom(s).

4. The quinuclidine derivative of claim 3, wherein the aromatic monocyclic heterocyclic group is furanyl, in particular 2- or 3-furanyl; thienyl, in particular 2- or 3-thienyl; selenophenyl, in particular 2- or 3-selenophenyl; pyrrolyl (azolyl), in particular 2 or 3-pyrrolyl; oxazolyl, in particular oxazol-2,4 or 5-yl; thiazolyl, in particular thiazol-2,4 or 5-yl; imidazolyl, in particular 2 or 4-imidazolyl; pyrazolyl, in particular 3 or 4-pyrazolyl; isoxazolyl, in particular isoxazol-3,4 or 5-yl; isothiazolyl, in particular isothiazol-3,4 or 5-yl; oxadiazolyl, in particular 1,2,3-oxadiazol-4 or 5-yl, or 1,3,4-oxadiazol-2-yl; triazolyl, in particular 1,2,3-triazol-4-yl or 1,2,4-triazol-3-yl; thiadiazolyl, in particular 1,2,3-thiadiazol-4 or 5-yl, or 1,3,4-thiadiazol-2-yl; pyridinyl, in particular 2,3 or 4-pyridinyl; pyridazinyl, in particular 3 or 4-pyridazinyl; pyrimidinyl, in particular 2,4 or 5-pyrimidinyl; pyrazinyl, in particular 2 or 3-pyrazinyl; and triazinyl, in particular 1,2,4- or 1,3,5-triazinyl.

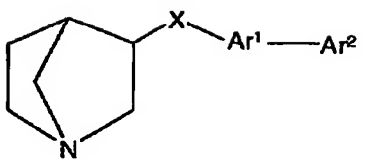
5. The quinuclidine derivative of claim 1, wherein the aromatic polycyclic heterocyclic group is a bi- or poly-heterocyclic group, which groups include benzo-fused 5- and 6-membered heterocyclic rings containing one or more heteroatoms, selected from nitrogen (N), oxygen (O) and/or sulphur (S).

6. The quinuclidine derivative of claim 5, wherein the bicyclic aromatic heterocyclic group is indolyl, in particular 2 or 3-indolyl; isoindolyl, in particular 1 or 3-isoindolyl; benzo[b]furanyl, in particular 2 or 3-benzo[b]furanyl; benzo[b]thienyl, in particular 2 or 3-benzo[b]thienyl; benzoimidazolyl, in particular 2-benzoimidazolyl; benzothiazolyl, in particular 2-benzothiazolyl; quinolinyl, in particular 2,3 or 4-quinolinyl; isoquinolinyl, in particular 1,3 or 4-isoquinolinyl; cinnolinyl, in particular 3 or 4-cinnolinyl; phthalazinyl, in particular 1 or 4-phthalazinyl; quinazolinyl, in particular 2 or 4-quinazolinyl; quinoxalinyl, in particular 2 or 3-quinoxalinyl.

7. The quinuclidine derivative of claim 5, wherein the polycyclic aromatic heterocyclic group is fluorenone, dibenzothiophene or dibenzothiophene-5,5-dioxide.

8. The quinuclidine derivative of any of claims 1-7, wherein the aromatic group is substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen.

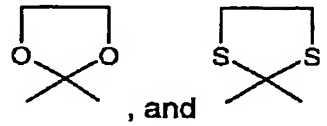
9. The quinuclidine derivative of claim 1, represented by Formula II



(II)

wherein

X represents a linker selected from -O-, -S-, $-CH_2-$, $-C(=CH_2)-$,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and ;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl; and

Ar^2 represents an optional aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl.

10. The quinuclidine derivative of claim 9, wherein

X represents O, S or CH_2; and

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic group selected from phenyl and naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic 5- or 6-membered monocyclic heterocyclic group selected from 1,3,4-thiadiazol-2-yl, pyridazinyl, in particular 2-pyridazinyl, which aromatic monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic bicyclic heterocyclic group selected from quinolinyl, in particular 2-quinolinyl; benzothiazolyl, in particular 2-benzothiazolyl; quinoxalinyl, in particular 2-quinoxalinyl; benzoimidazolyl, in particular 2-benzoimidazolyl; and benzoxazolyl, in particular 2-benzoxazolyl, which aromatic bicyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; and

Ar^2 represents phenyl or naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen.

11. The quinuclidine derivative of claim 9, wherein

X represents O, S or CH_2; and

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic group selected from phenyl and naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

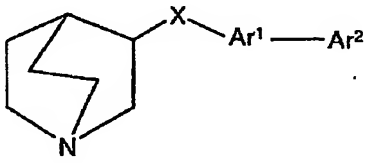
Ar^1 represents an aromatic 5- or 6-membered monocyclic heterocyclic group selected from 1,3,4-thiadiazol-2-yl, pyridazinyl, in particular 2-pyridazinyl, which aromatic monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic bicyclic heterocyclic group selected from quinolinyl, in particular 2-quinolinyl; benzothiazolyl, in particular 2-benzothiazolyl; quinoxalinyl, in particular 2-quinoxalinyl; benzoimidazolyl, in particular 2-benzoimidazolyl; and benzoxazolyl, in particular 2-benzoxazolyl, which aromatic bicyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents a polycyclic aromatic heterocyclic group selected from fluorenone, dibenzothiophene or dibenzothiophene-5,5-dioxide; and

Ar^2 is absent.

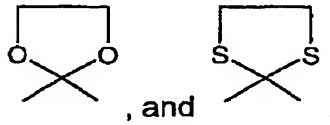
12. The quinuclidine derivative of claim 1, represented by Formula III



(III)

wherein,

X represents a linker selected from -O-, -S-, $-CH_2-$, $-C(=CH_2)-$,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and ;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl; and

Ar^2 represents an optional aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, and sulfamoyl.

13. The quinuclidine derivative of claim 12, wherein

X represents O, S or CH_2;

Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic group selected from phenyl and naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic 5- or 6-membered monocyclic heterocyclic group selected from 1,3,4-thiadiazol-2-yl, pyridazinyl, in particular 2-pyridazinyl, which aromatic monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or

Ar^1 represents an aromatic bicyclic heterocyclic group selected from quinolinyl, in particular 2-quinolinyl; benzothiazolyl, in particular 2-benzothiazolyl; quinoxalinyl, in particular 2-quinoxalinyl; benzoimidazolyl, in particular 2-benzoimidazolyl; and benzoxazolyl, in particular 2-benzoxazolyl, which aromatic bicyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; and

Ar^2 represents phenyl or naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen.

14. The quinuclidine derivative of claim 13, which is

3-(Biphenyl-4-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(Biphenyl-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(Biphenyl-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(5-Phenyl-[1,3,4]oxadiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(5-Phenyl-[1,3,4]thiadiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(2-Phenyl-pyrimidin-5-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(5-Phenyl-pyrimidin-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

3-(6-Phenyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
3-(6-Benzyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
3-(6-Phenoxy-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane; or
3-(6-Phenylsulfanyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
or an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

15. The quinuclidine derivative of claim 12, wherein
X represents O, S or CH_2; and
Ar^1 represents an aromatic monocyclic or polycyclic, carbocyclic group selected from phenyl and naphthyl, which aromatic carbocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or
Ar^1 represents an aromatic 5- or 6-membered monocyclic heterocyclic group selected from 1,3,4-thiadiazol-2-yl, pyridazinyl, in particular 2-pyridazinyl, which aromatic monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or
Ar^1 represents an aromatic bicyclic heterocyclic group selected from quinolinyl, *in particular 2-quinolinyl*; benzothiazolyl, *in particular 2-benzothiazolyl*; quinoxalinyl, in particular 2-quinoxalinyl; benzoimidazolyl, in particular 2-benzoimidazolyl; and benzoxazolyl, in particular 2-benzoxazolyl, which aromatic bicyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, alkoxy and halogen; or
Ar^1 represents a polycyclic aromatic heterocyclic group selected from fluorenone, dibenzothiophene or dibenzothiophene-5,5-dioxide; and
Ar^2 is absent.

16. The quinuclidine derivative of claim 15, which is
(±)-3-(Naphthalen-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Benzoxazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Chloro-benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1*H*-Benzoimidazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1-Methyl-1*H*-benzoimidazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Isoquinolin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoline;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinazoline;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoxaline;
(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-3-methoxy-quinoxaline;

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-3-chloro-quinoxaline;
(±)-3-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-cinnoline; or
(±)-3-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-benzo[1,2,4]triazine;
or an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

17. A pharmaceutical composition comprising a therapeutically effective amount of the quinuclidine derivative of any of claims 1-16, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

18. Use of the quinuclidine derivative of any of claims 1-16, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the action of a nicotinic acetylcholine receptor modulator.

19. The use according to claim 18, wherein the disease, disorder or condition to be treated is a disease or disorder of the central nervous system, a disease or disorder caused by or related to smooth muscle contraction, an endocrine disorder, a disease or disorder caused by or related to neuro-degeneration, a disease or disorder caused by or related to inflammation, pain, a withdrawal symptom caused by the termination of abuse of chemical substances.

20. The use according to claim 19, wherein the disease or disorder of the central nervous system is anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourettes syndrome, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, dementia, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, chronic fatigue syndrome, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

21. The use according to claim 19, wherein the disease or disorder caused by or related to smooth muscle contraction is convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

22. The use according to claim 19, wherein the endocrine disorder is thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

23. The use according to claim 19, wherein the neuro-degenerative disease is transient anoxia and induced neurodegeneration.

24. The use according to claim 19, wherein the disease or disorder caused by or related to inflammation is an inflammatory skin disorder such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

25. The use according to claim 19, wherein pain is a mild, a moderate or a severe pain of acute, chronic or recurrent character, a pain caused by migraine, a postoperative pain, or a phantom limb pain.

26. The use according to claim 19, wherein the addictive substance is a nicotine containing product such as tobacco, an opioids such as heroin, cocaine or morphine, a benzodiazepine or a benzodiazepin-acting drug, or alcohol.

27. A method of the treatment or alleviation of a disease or disorder of a living animal body, including a human, which disease or disorder is responsive to the action of a nicotinic acetylcholine receptor modulator, which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of the quinuclidine derivative according to any of claims 1-16.

ABSTRACT

NOVEL QUINUCLIDINE DERIVATIVES AND THEIR USE

This invention relates to novel quinuclidine derivatives and their use as pharmaceuticals.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.